**Written Testimony of Steven Walker**
**(with references and attachments)**
**Abigail Alliance for Better Access to Developmental Drugs**

**Discussion Drafts of Legislation on PDUFA, MDUFMA, Drug Safety, Pediatric Safety, Pediatric Incentive, and Pediatric Devices**

**Energy and Commerce Committee**
**Subcommittee on Health**
**June 12, 2007**

Mr. Chairman, Congressman Deal and members of the Committee, we at the Abigail Alliance wish to express our thanks for this hearing, and for inviting us to testify.

My name is Steven Walker, Co-Founder and Chief Advisor to the Abigail Alliance. I receive no compensation for my efforts as an advocate, and I pay my own expenses. *(See Attachment A, S.O.S. to the FDA, editorial in the Wall Street Journal, August 26, 2003, by Steven Walker)*

The Abigail Alliance for Better Access to Developmental Drugs is a non-profit, non-partisan patient advocacy organization dedicated to serving the needs of people suffering from serious and life-threatening diseases.

Based on our first-hand experience with the harsh regulatory realities faced by patients with life-threatening diseases, we have proposed a solution called Tier 1 initial Approval to ease the regulatory barriers our constituents face, while simultaneously protecting the clinical trials system. Tier 1 was submitted to the FDA in a Citizens Petition four years

ago, yesterday. We are still waiting for a response. *(Our Citizens Petition and related information can be found at www.abigail-alliance.org.)*

Last year a bill called the Access Act based on our Tier 1 proposal was introduced in both houses of Congress. It is going to be reintroduced this year and we strongly urge Congress to pass the bill. Incidentally, legislation to address the needs of our constituents should have been included in the discussion drafts today. *(The legislation as introduced in the Senate in the 109th Congress is posted at www.abigail-alliance.org. The house version was identical.)*

In July 2003, we filed a suit against the FDA in federal court, claiming that the FDA's denial of access to promising investigational drugs for patients with no other option but death from their disease, violates their Constitutional rights of due process and privacy. Last year, a three judge panel of the DC Federal Court of Appeals agreed, but the FDA moved for rehearing by the full appeals court, and almost four years after filing the suit, we are still awaiting a trial on the merits of our claim. *(The original lawsuit is posted at www.abigail-alliance.org. The opinion issued last year by the three-judge panel of the DC Federal Court of Appeals is provided in Attachment B. For more information on the status of the lawsuit see Attachment C, Drug Czars, editorial in the Wall Street Journal on May 4, 2007 by Steven Walker)*

Over those four years 2.2 million Americans died from cancer alone. This is not just a regulatory policy issue. It is a major civil rights issue.

**Clinical Trial Registry Database**

Turning to the discussion drafts, the Abigail Alliance has long sought readily available and more complete listings of clinical trials and access programs for investigational drugs, and we support the proposed clinical trials registry in the discussion draft.

**Clinical Trial Results Database**

We also support in concept, the idea of making the results of clinical trials public, but we think the clinical trial results database as proposed in the discussion draft has all the earmarks of a major regulatory misstep. The evidence for this can be found in the recent flap over Avandia. The publication of scientifically-weak, meta-analysis results in the New England Journal of Medicine was a statistical "drive-by" hit on the integrity of our regulatory system. If the results database is enacted as proposed, the FDA will become the regular target of poorly-constructed statistical hand-grenades, and spend far too much of its time trying to clean up the mess after each one explodes in sensational fashion in the media.

Consequently, we ask that the committee remove the clinical trial results database from the discussion draft, and schedule future hearings to receive additional input on how to make trial results public while at the same time preserving the integrity of our regulatory system.

**Food and Drug Administration Advisory Panels Conflicts of Interest**

On conflicts of interest on advisory committees, we think the draft legislation is putting the cart before the horse.

The Federal Advisory Committee Act prohibits inappropriate influence by the appointing authority over its advisory committees, but FDA review office directors are empowered to manipulate the ideological makeup of their advisory committees, and potentially use that power to pursue the outcome they want regarding policy matters and votes on specific drugs. We believe this has in fact happened with some cancer drugs. *(See Attachment D, Slides from Presentation to the Oncologic Drugs Advisory Committee, September 6, 2006, ODAC and the FDA, Arms-Length or Arm-In-Arm?, by Steven Walker; and Attachment C, Drug Czars, editorial in the Wall Street Journal, May 4, 2007, by Steven Walker)*

Congress should start by looking at the FDA's process for selecting advisory committee members and for now, table the secondary conflict of interest issue.

**Risk Evaluation and Mitigation Strategies**

We oppose the proposal to require mandatory risk evaluation and mitigation strategies, or REMS, because they are mandatory, making them yet another one-size-fits-all solution

that won't work. The FDA already has and uses the authority to impose what they call Risk Management Plans or RiskMAPs on drugs at the time of approval. RiskMAPs have so far been a mixed bag of prudent controls burdened with unnecessary approval delays and prescribing restrictions, coupled with requirements for highly-unethical post-approval clinical trials. RiskMAPs also have resulted in major intrusions by the FDA into the practice of medicine. Mandatory REMS, even though proposed as being flexible, are likely to evolve quickly into an over-applied defensive mechanism for FDA instead of its intended use of being a rational, sober post-marketing monitoring tool. We need, post-market monitoring of drugs, but we do not need any more one-size-fits-all solutions. We suggest that the flexible model for what must be included in a REMS be used to replace the current RiskMAP model, but that the need for a REMS be determined on a case-by-case basis.

**The Reagan-Udall Institute for Applied Biomedical Research**

We think the Udall-Reagan Institute is a good idea that could be made even better. The goal is regulatory modernization, and that can only come through real change in the way the FDA does it job. Consequently, the institute should be moved inside the FDA and given line authority to issue new policies and guidance, and to initiate rulemaking. *(For more information on the Abigail Alliance positions on what is wrong and how to modernize and improve the science and regulatory policies of the FDA, see Attachment E, Making FDA Work for Patients, Legal Backgrounder, Vol. 20, No. 10. Washington Legal Foundation., February 25, 2005; and Attachment F, Decelerated Approval,*

*Presentation to the Oncologic Drugs Advisory Committee, by Steven Walker, November 8, 2005)*

**Closing Comments**

This entire debate regarding FDA reform has its roots in a decades-old feud raging within the FDA and the medical research community between two groups of statisticians: those who believe in the forward-looking trials used for pre-approval testing, and those who support the backward-looking trials that try to find drug safety needles in haystacks.

Neither statistical camp should win this feud. Patients should win, and for that to happen, we need to move away from the rigid, often unethical statistical approaches we have now, and move toward real science.

We need to remember that FDA's mission is not to control and punish the drug companies, but rather to protect and promote the public health, and it is on the "promote" side where will find better treatments and cures for diseases like cancer.

I would like to close with an important fact. Every investigational drug for which the Abigail Alliance has sought early access was eventually approved by the FDA. We knew that patients would be better off if they could get the drug than if they could not, usually years before the FDA acted to make those drugs available. If the FDA was less a barrier

to progress, millions more would have gained access to that progress over the last seven years.

Thank you, and of course when the opening statements are concluded, I would be happy to answer your questions.

# Attachment A

S.O.S to the FDA

Editorial in the Wall Street Journal
By Steven Walker

August 26, 2003

THE WALL STREET JOURNAL. ONLINE



August 26, 2003

COMMENTARY

# S.O.S. to the FDA



**By STEVEN WALKER**
*August 26, 2003*

Our Food and Drug Administration is often praised for establishing the "gold standard" for drug approvals. If it is FDA-approved, folks say, all can be sure that the drug has been rigorously shown to be safe and effective through years of careful review. Unfortunately, the people making this claim increasingly work at the FDA. Those waiting for FDA decisions, mainly dying patients and those who care for them, view the agency as a barrier to new treatments that they desperately need to live. The agency's inability to recognize and adjust to the accelerating pace of medical research has tarnished its gilt.

Never has this been more evident than now. At a recent major cancer research meeting in Chicago, two announcements were made regarding breakthrough drugs for colon cancer, the second leading cause of cancer deaths in the U.S. (According to the American Cancer Society it will kill 57,000 this year.) The first drug is Imclone Systems Inc.'s Erbitux, the not-so-new targeted drug that is inexplicably more famous for its ill-conceived rejection by the FDA in December 2001 and the ensuing scandals than for its effectiveness as a cancer drug.

Erbitux has once again been shown to be an important advance in treating colon cancer. Results of the latest trials are identical to the results the FDA rejected in 2001, and they more than meet the FDA's current standards for accelerated approval. Since the rejection, about 80,000 Americans have died from colon cancer without getting Erbitux. Erbitux shrank tumors for about 23% of patients for whom nothing else would work, and controlled the cancer for an average of four-plus months. Considering that the best FDA-approved treatment for colon cancer only controls tumors for about 10 months, adding this drug to the arsenal as a follow-up treatment is a major advance.

* * *

I know from direct observation how well Erbitux can work. Near death in September 2002, my wife Jennifer managed to enroll in a small clinical trial for Erbitux. The treatment lifted her off her deathbed in two days, resolved the symptoms of her cancer in two weeks, and allowed us to return to a normal life, skiing, hiking and working. Many patients in the trial experienced similar results. The sole side effect was a tolerable skin rash. Erbitux worked for six months. It stopped working in March this year. Out of accessible options to control her cancer, Jennifer died in June -- knowing that she was being denied access, by a plodding government agency, to even newer investigational drugs that might have further extended her life.

Another drug, whose results were kept secret by its sponsor and the FDA until the Chicago cancer

meeting in June, is Avastin, a drug developed by Genentech. It extends the effectiveness of the first-line treatment given to colon cancer patients by more than four months, and extends survival by four months too, with almost no increase in side-effects when given in combination with the approved first-line treatment known as the Saltz regimen. Although not yet comprehensively tested in late-stage, resistant cancer patients, Avastin might have been useful to Jennifer and thousands of others had they been able to try it in combination with other drugs.

So just like that, we now have the ability to extend the lives of colon cancer patients by an average of more than eight months (or in some cases longer), a significant increase when considering that advanced colon cancer patients can expect to live little more than a year. Tragically, patients can't get Erbitux or Avastin because of the FDA's antiquated approach to recognizing and approving cancer drugs. The key to availability of any new drug is approval by the FDA, and neither drug is likely to be approved sooner than early next year. The drugs can't be purchased for any price, and aren't available outside small clinical trials and a small expanded access program for Erbitux. The FDA has six months to review Avastin and Erbitux from the date they receive complete applications. The application for Erbitux was submitted on Aug. 14, and an application has yet to be submitted for Avastin. Before blaming the companies for the time they are taking to file their paperwork, understand that the FDA is a notoriously nitpicky agency, concentrating on the most minor details even when those are not relevant to those who will be treated with the drug. Americans shouldn't die, for example, because the FDA is hung up on a few words in the package labeling.

The great majority of those finding out they have advanced colon cancer in the coming months will not get Avastin with their first-line treatment, costing them an average of at least four months of life. Nearly all of those finding out that their cancers will no longer respond to the existing approved treatments will be denied access to Erbitux, costing them at least four months of control of their disease. Some might quickly blame the companies for not giving the drugs away, and the FDA will claim they would allow this if the companies would do it, but no company can afford to treat thousands of patients for free with drugs that cost hundreds of millions to develop, produce and administer.

So just like that, two significant victories in our war on cancer will be denied to cancer patients. Using a conservative estimate based on American Cancer Society numbers for new cases and deaths, and the clinical trial results, about 14,500 Americans will be denied Avastin and about 28,500 will be denied Erbitux over the next six months while the FDA waits for and processes paperwork, assuming it reviews the applications quickly, by no means a certain prospect. The cost in human life adds up to about 14,300 years. If approval takes longer the losses will mount. The actual cost in life will be further increased because off-label use for patients with other forms of cancer will also be precluded. The situation with Erbitux and Avastin is not isolated. It is business as usual.

At the FDA, the process and strict adherence to regulations, guidance and policy always comes first, and the agency's power over availability of drugs is absolute. My wife's battle with cancer and the setbacks she suffered at the hands of the system are typical of the challenges faced by all Americans fighting life-threatening diseases. Too many people are dying at the hands of a bureaucracy that does not have an approval mechanism that could ease the loss of life.

We at the Abigail Alliance for Better Access to Developmental Drugs and the Washington Legal Foundation have given them one. Called "Tier 1 Initial Approval," it lowers the barriers imposed on cancer patients by the FDA's gold standard. It would give the agency the ability to respond to those with immediate needs without weakening its ability to ensure that new drugs are safe and

effective. In fact, it would strengthen our drug development system, forcing it to be more responsive to the patients it exists to serve.

As Mark McClellan, the new FDA commissioner, continues his efforts to repair inherited problems with the regulatory process, he also should race to modernize his agency from the ground up. Doing less will render his agency incapable of keeping pace with accelerating medical breakthroughs that are already transforming the prospects of some ill Americans from despair, to hope, to life. Some will oppose him vigorously because old ways die hard.

We are finally beginning to win the war on cancer. The cancer patients have always been courageous foot soldiers in the fight, contributing mightily in clinical trials to get us here. It is now time to see if there are heroes at the FDA with the vision, courage and resolve to clean the tarnish from our gold standard. A lot of lives -- and very possibly yours -- depend on it.

***Mr. Walker, adviser to the Abigail Alliance for Better Access to Developmental Drugs, is the husband of the late Jennifer I. McNeillie.***

# Attachment B

Opinion of the

United States Court of Appeals
For the District of Columbia Circuit

Abigail Allianced v von Eschenbach

Decided May 2, 2006

# United States Court of Appeals

**FOR THE DISTRICT OF COLUMBIA CIRCUIT**

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Argued October 21, 2005 Decided May 2, 2006

No. 04-5350

ABIGAIL ALLIANCE FOR BETTER ACCESS TO DEVELOPMENTAL DRUGS AND WASHINGTON LEGAL FOUNDATION,
APPELLANTS

v.

ANDREW C. VON ESCHENBACH, M.D.,
IN HIS OFFICIAL CAPACITY AS ACTING COMMISSIONER,
FOOD AND DRUG ADMINISTRATION AND
MICHAEL O. LEAVITT,
IN HIS OFFICIAL CAPACITY AS SECRETARY,
U.S. DEPT. OF HEALTH AND HUMAN SERVICES,
APPELLEES

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Appeal from the United States District Court
for the District of Columbia
(No. 03cv01601)

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*James S. Ballenger* argued the cause for appellants. With him on the briefs were *Daniel J. Popeo* and *David Price*.

*Richard A. Samp* entered an appearance.

*Rhonda C. Fields*, Assistant U.S. Attorney, argued the cause for appellee. With her on the brief were *Kenneth L. Wainstein*, U.S. Attorney, *Michael J. Ryan*, Assistant U.S. Attorney, *Eric M. Blumberg*, Deputy Chief Counsel, U.S. Department of Health and Human Services, and *Karen E. Schifter*, Associate Chief Counsel. *R. Craig Lawrence*, Assistant U.S. Attorney, entered an appearance.

Before: GINSBURG, *Chief Judge*, and ROGERS and GRIFFITH, *Circuit Judges*.

Opinion for the Court filed by *Circuit Judge* ROGERS.

Dissenting opinion filed by *Circuit Judge* GRIFFITH.

ROGERS, *Circuit Judge*: The Abigail Alliance for Better Access to Developmental Drugs ("the Alliance") seeks to enjoin the Food and Drug Administration ("FDA") from continuing to enforce a policy barring the sale of new drugs that the FDA has determined, after Phase I trials on human beings, are sufficiently safe for expanded human testing (hereafter "post-Phase I investigational new drugs"). More specifically, the Alliance seeks access to potentially life-saving post-Phase I investigational new drugs on behalf of mentally competent, terminally ill adult patients who have no alternative government-approved treatment options (hereafter "terminally ill patients"). The Alliance contends that the FDA's policy violates the substantive due process rights to privacy, liberty, and life of its terminally ill members. The complaint presents the question of whether the Due Process Clause protects the right of terminally ill patients to decide, without FDA interference, whether to assume the risks of using potentially life-saving investigational new drugs that the FDA has yet to approve for commercial

marketing but that the FDA has determined, after Phase I clinical human trials, are safe enough for further testing on a substantial number of human beings.

Upon applying the Supreme Court's test for addressing substantive due process claims set forth in *Washington v. Glucksberg*, 521 U.S. 702, 710 (1997), we hold that the district court erred in dismissing the Alliance's complaint pursuant to Federal Rule of Civil Procedure 12(b)(6) for failure to state a claim. First, the right at issue, carefully described, is the right of a mentally competent, terminally ill adult patient to access potentially life-saving post-Phase I investigational new drugs, upon a doctor's advice, even where that medication carries risks for the patient. Second, we find, upon examining "our Nation's history, legal traditions, and practices," *Glucksberg*, 521 U.S. at 710, that the government has not blocked access to new drugs throughout the greater part of our Nation's history. Only in recent years has the government injected itself into consideration of the effectiveness of new drugs. Third, Supreme Court precedent on liberty indicates that the right claimed by the Alliance can be inferred from the Court's conclusion in *Cruzan v. Director, Missouri Department of Health*, 497 U.S. 261, 278 (1990), that an individual has a due process right to refuse life-sustaining medical treatment, *id*. at 279. Here, the claim implicates a similar right — the right to access potentially life-sustaining medication where there are no alternative government-approved treatment options. In both instances, the key is the patient's right to make the decision about her life free from government interference.

Because the question remains whether the FDA's challenged policy has violated that right, we reverse the dismissal of the Alliance's complaint and remand the case to the district court to determine whether the FDA's policy "is narrowly tailored to serve a compelling [governmental]

interest." *Glucksberg*, 521 U.S. at 721 (quoting *Reno v. Flores*, 506 U.S. 292, 302 (1993)).

In Part I, we set forth the background to this appeal. In Part II, we examine Supreme Court precedent indicating how substantive due process rights are to be discerned. So guided, we consider, in Part III, whether the Alliance's claimed right warrants protection under the Due Process Clause.

## I.

### A.

The Food, Drug, and Cosmetic Act ("FDCA"), Pub. L. No. 75-717, §§ 1-902, 52 Stat. 1040 (1938) (codified as amended at 21 U.S.C. § 301 *et seq*. (2000)), prohibits drug manufacturers from introducing any "new drug" into interstate commerce until manufacturers have applied for, and received, FDA approval. 21 U.S.C. § 355(a). A "new drug" is any substance covered by the FDCA not "generally recognized, among experts . . . as safe and effective for use under the conditions prescribed . . . in the labeling." 21 U.S.C. § 321(p)(1); *see also United States v. 50 Boxes More or Less*, 909 F.2d 24 (1st Cir. 1990). Before a new drug is eligible for full approval and marketing, the Secretary of the U.S. Department of Health and Human Services must find "substantial evidence that the drug will have the effect it purports or is represented to have." 21 U.S.C. § 355(d). Exempted from this general ban are new drugs "intended solely for investigational use by experts . . . ." *Id.* § 355(i)(1).

The FDCA directs the Secretary to promulgate regulations for testing new drugs. *Id.* Pursuant to this authority, the FDA has promulgated regulations that require three phases of government testing on humans before investigational new drugs can receive FDA approval and enter the commercial marketplace. In Phase I, new drugs are tested on 20 to 80

human subjects to determine "the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness." 21 C.F.R. § 312.21(a). It takes approximately one year to conduct Phase I testing.[1] FDA counsel acknowledged at oral argument that drugs that survive this phase have been deemed "sufficiently safe for substantial human testing, but [are] not yet proven to be safe and effective to the satisfaction of the FDA [to be commercially marketed]." Oral Argument Tape of Oct. 21, 2005 at 15:57-15:59. Phase II involves targeted, controlled clinical studies of up to several hundred human subjects "to evaluate the effectiveness of the [Phase I investigational new] drug . . . and to determine the common short-term side effects and risks associated with the drug." 21 C.F.R. § 312.21(b). Phase III expanded trials, which can include several thousand human subjects, are "performed after preliminary evidence suggesting effectiveness of the drug has been obtained, and are intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug . . . ." *Id.* § 312.21(c). With narrow exceptions, FDA regulations require informed consent to be obtained from clinical trial participants. *Id*. §§ 50.1-50.27.

**B.**

On January 16, 2003, the Alliance submitted a proposal to the FDA for new regulations to render post-Phase I investigational new drugs available to terminally ill patients who were not admitted to the FDA's clinical trials. The FDA rejected the proposal by letter dated April 25, 2003, outlining the FDA's policy. On June 11, 2003, Alliance filed a Citizen Petition, pursuant to 21 C.F.R. § 10.30, challenging the FDA's

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[1] *See* Alison R. McCabe, *A Precarious Balancing Act—The Role of the FDA as Protector of Public Health and Industry Wealth*, 36 SUFFOLK U. L. REV. 787, 790 n.26 (2003).

policy barring the sale of investigational new drugs that have successfully completed Phase I trials to terminally ill patients not selected for clinical trials. The FDA acknowledged receipt of the Citizen Petition but otherwise did not respond within 180 days, thereby entitling the Alliance to seek judicial review of the challenged policy. *See id*. § 10.30(e)(2).

The Alliance filed suit against the FDA Commissioner and the Secretary of the Department of Health and Human Services, seeking to enjoin the FDA from enforcing the policy barring the sale of post-Phase I investigational new drugs to terminally ill patients not in Phase II clinical trials. Noting that the FDA has administrative discretion to define several stages for human testing of new drugs after animal testing has been conducted, the complaint alleges that it takes, on average, just under seven years for investigational new drugs to complete the three phases of clinical human trials and receive FDA approval for commercial marketing and thus become eligible for purchase by persons not in FDA clinical trials. Compl. ¶ 12.[2] The complaint also alleges that non-commercial options provide relief only to a very small number of terminally ill patients as spaces in clinical trials are "very limited . . . in relation to the need." Compl. ¶ 15. The Alliance asserts that clinical human trials are limited in number and by type of patient who qualifies. Further, the FDA's "compassionate use" programs, which permit drug companies voluntarily to provide new drugs at cost during the pre-approval period, are available only to "a fraction of those in desperate need." *Id.* Although the FDA may permit "treatment use" of unapproved new drugs, *see* 21 C.F.R. § 312.34 (1999), and has allowed access for limited groups of persons with

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[2] *See also* Christopher P. Adams & Van V. Brantner, *New Drug Development: Estimating Entry from Human Clinical Trials* 9 (July 7, 2003), *available at* http://www.ftc.gov/be/workpapers/wp262.pdf.

AIDS,[3] the FDA has refused as a general matter to allow terminally ill patients to have access to investigational new drugs that have successfully completed Phase I trials. Consequently, the complaint alleges, the effect of the FDA policy, as illustrated by the examples of the deaths of four terminally ill patients, has been to deny terminally ill patients the choice to use post-Phase I investigational new drugs despite the patients' willingness "to assume risks if their physicians advise them that a treatment may save or prolong their lives and if they have no other viable options." Compl. ¶¶ 16, 18. Prior to discovery, the FDA moved to dismiss the complaint, and, alternatively, for summary judgment. The Alliance responded by filing an opposition and its own motion for summary judgment.

The district court dismissed the complaint pursuant to Rule 12(b)(6) for failure to state a claim. The court rejected the Alliance's argument that it sought no "new" right but only recognition and enforcement of the right to life that is explicitly guaranteed by the Due Process Clause, observing that no court decision has "extended the Due Process Clause to cover a terminally ill patient's right to receive medical treatment." Mem. Op. of Aug. 30, 2004, at 18 (emphasis deleted). Although acknowledging "the Nation's longstanding legal tradition . . . to attempt to preserve life," *id*., the district court stated that in *Glucksberg*, the Supreme Court had distinguished some "personal" decisions from others, 521 U.S. at 727, and that the Alliance could not "possibl[y] claim that the specific right claimed has a long-standing tradition." Mem. Op. at 18. The district court also rejected the Alliance's argument that the Supreme Court's recognition in *Cruzan* of the right to choose

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[3] *See* Michael D. Greenberg, *AIDS, Experimental Drug Approval, and the FDA New Drug Screening Process*, 3 N.Y.U. J. LEGIS. & PUB. POL'Y 295, 315-20 (1999-2000).

death by refusing medical treatment implied a complementary right to choose life by obtaining potentially life-saving medication. In the district court's view, the Alliance sought recognition of "an entirely different sort of right [from that recognized in *Cruzan*] — not freedom from government imposition, but an affirmative right of access to medical treatment." *Id*. at 19. In the absence of due process protection for terminally ill patients seeking access to potentially life saving post-Phase I drugs, the district court concluded that the challenged FDA policy is rationally related to a legitimate governmental interest.

The Alliance appeals, and our review is *de novo*.[4] *See Cicippio-Puleo v. Islamic Republic of Iran,* 353 F.3d 1024, 1031-32 (D.C. Cir. 2004). We treat the dismissal of the complaint as occurring pursuant to Rule 12(b)(6), notwithstanding the district court's consideration of the FDA's April 23, 2003 letter because the letter's conclusion was alleged in the complaint and the FDA does not dispute its contents. *See Gryl ex rel. Shire Pharms. Group PLC v. Shire Pharms. Group PLC*, 298 F.3d 136, 140 (2d Cir. 2002); *Pryor v. Nat'l Collegiate Athletic Ass'n*, 288 F.3d 548, 560 (3d Cir. 2002) (citing 62 Fed. Proc. L. Ed. § 62:508). *Cf. Settles v. United States Parole Comm'n*, 429 F.3d 1098, 1107 (D.C. Cir. 2005).

A court should not dismiss a complaint pursuant to Rule 12(b)(6) for failure to state a claim "unless it appears beyond doubt that the plaintiff can prove no set of facts in support of his claim which would entitle him to relief." *Conley v. Gibson*, 355 U.S. 41, 45-46 (1957); *Warren v. District of Columbia*, 353 F.3d 36, 37 (D.C. Cir. 2004). In determining the sufficiency of the

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[4] The Washington Legal Foundation is also a named appellant, but conceded at oral argument that it lacked Article III standing.

complaint, this court reviews questions of law *de novo* while treating the complaint's factual allegations as true and granting the plaintiff the benefit of all reasonable inferences from the facts alleged. *See Conley,* 351 U.S. at 45-46; *Sparrow v. United Air Lines, Inc.*, 216 F.3d 1111, 1114 (D.C. Cir. 2000).

**II.**

The Due Process Clause of the Fifth Amendment to the United States Constitution provides that "[n]o person shall be . . . deprived of life, liberty, or property, without due process of law." U.S. CONST. AMEND. V. The Supreme Court has held that the Clause "guarantees more than fair process" and accords substantive protection to the rights it guarantees. *See Troxel v. Granville*, 530 U.S. 57, 65 (2000) (plurality opinion); *Glucksberg*, 521 U.S. at 719; *Flores*, 507 U.S. at 301-02. Substantive due process claims can present difficulties for courts. *See Michael H. v. Gerald D.*, 491 U.S. 110, 121 (1989) (plurality opinion); *Moore v. City of East Cleveland*, 431 U.S. 494, 502 (1977). In a case of first impression where fundamental rights may be at stake, determining the limits of the government's authority over an individual's freedom to make certain personal decisions unavoidably entails a careful and possibly arduous assessment of that personal decision's objective characteristics in order to determine whether it warrants protection under the Due Process Clause. *Cf. Roberts v. U.S. Jaycees*, 468 U.S. 609, 620 (1984). Nonetheless, the district court appears to have viewed its role as unduly constrained. Pointing to an advisory cautioning in *Dronenburg v. Zech*, 741 F.2d 1388, 1396 (D.C. Cir. 1984), that lower courts "should [not] freely create new constitutional rights" without "guidance from the Constitution or . . . from articulated Supreme Court principle," the district court focused on the absence of binding precedent recognizing the substantive due process right claimed by the Alliance. Since *Dronenberg,* the Supreme Court

has provided guideposts to enable a court to assess the merits of the Alliance's claim.[5]

Although the Supreme Court has never explicitly said so, and we need not decide the matter here, it appears the Supreme Court has employed two distinct approaches when faced with a claim to a fundamental right. In some cases, the Court has discerned the existence of fundamental rights by probing what "personal dignity and autonomy" demand. *See Planned Parenthood of Southeastern Pa. v. Casey*, 505 U.S. 833, 851 (1992) (citations omitted). In other cases, the Court has derived fundamental rights by reference to the Nation's history and legal tradition, *see, e.g., Glucksberg*, 521 U.S. 702.[6] The line of cases beginning with *Griswold v. Connecticut*, 381 U.S. 479 (1965), and continuing through *Eisenstadt v. Baird*, 405 U.S. 438 (1972), *Roe v. Wade*, 410 U.S. 113 (1973), and *Casey*, 505 U.S. 833, follow the first approach with their heavy reliance on the concepts of individual rights to autonomy and self-determination, and in their unwillingness to countenance state intrusion into certain protected domains such as the bedroom, the clinic, and the womb. This approach is succinctly captured by *Casey*'s characterization of substantive due process rights as those that involve "the most intimate and personal choices a person may make in a lifetime, choices central to personal dignity and autonomy." *Casey*, 505 U.S. at 851.

The other approach for determining whether a claimed right

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[5] The dissent, to the extent it presupposes the only liberties protected by the Constitution are those that have been explicitly recognized by the Supreme Court, *see* Dissent at 13 & n.3, is in error.

[6] *See* Robert C. Post, *The Supreme Court, 2002 Term—Foreword: Fashioning the Legal Constitution: Culture, Courts, and Law*, 117 HARV. L. REV. 4, 89 (2003).

warrants substantive due process protection, which appears to be more restrictive,[7] has two "features." *See Glucksberg*, 521 U.S. at 720. Under *Glucksberg*, courts must inquire whether the fundamental right asserted is "objectively, 'deeply rooted in this Nation's history and tradition,'" *id*. at 721 (quoting *Moore*, 431 U.S. at 503; *Snyder v. Massachusetts*, 291 U.S. 97 (1934)),[8] and

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[7] Post, *supra* note 6, at 91-93; Laurence H. Tribe, Lawrence v. Texas: *The "Fundamental Right" That Dare Not Speak its Name*, 117 HARV. L. REV. 1893, 1921-23 (2004).

[8] The Supreme Court's mention in *Lawrence v. Texas*, 539 U.S. 558, 592 (2003), of the "emerging awareness" regarding the liberty to engage in homosexual conduct does not limit the swath of time to be surveyed in a *Glucksberg* analysis of history and tradition. The reference to "laws and tradition in the past half century" appears in support of the Court's decision to depart from stare decisis and overrule *Bowers v. Hardwick*, 478 U.S. 186 (1986). Discrediting *Bowers*'s "sweeping references" to history thus had a purpose in addition to that addressed by the *Glucksberg* analysis: it is intended to show that not only had the Court in *Bowers* misread history but that it also had ignored modern trends giving protection to conduct that had long avoided criminal proscription in the states. *See Lawrence,* 539 U.S. at 568. Reading *Lawrence* as narrowing the *Glucksberg* historical inquiry to the last half century would gut the purpose of the *Glucksberg* test, which is to prevent the creation of substantive due process rights by forcing courts to accord due process protection only to those rights with a strong foundation in tradition. Other circuits have either treated the *Glucksberg* analysis as controlling after *Lawrence, see Fields v. Palmdale School Dist*., 427 F.3d 1197 (9th Cir. 2005); *Fields v. Legacy Health System*, 413 F.3d 943 (9th Cir. 2005); *Doe v. City of Lafayette, Ind*., 377 F.3d 757, 768 (7th Cir. 2004), or viewed *Lawrence* as not, properly speaking, a substantive due process decision, *see Lofton v. Sec'y of Dep't of Children and Family Servs*., 358 F.3d 804, 815-16 (11th Cir. 2004); *Muth v. Frank*, 412 F.3d 808, 818 (7th Cir. 2005). No court has regarded *Lawrence* as cabining *Glucksberg*.

"implicit in the concept of ordered liberty, such that neither liberty nor justice would exist if [it] were sacrificed," *Glucksberg*, 521 U.S. at 721 (quoting *Palko v. Connecticut*, 302 U.S. 319, 325-26 (1937)) (internal quotation marks omitted). Additionally, in order to ensure that courts do not multiply rights without principled boundaries, courts must provide a "careful description of the fundamental liberty interest." *Id*. at 721-23. If a court concludes that the claimed right is a fundamental right entitled to protection under the Due Process Clause, then the burden shifts to the government to show that its encroachment upon the right "is narrowly tailored to serve a compelling [governmental] interest." *Id.* at 721 (quoting *Flores*, 507 U.S. at 302).

Because we conclude, upon applying the seemingly more restrictive analysis of *Glucksberg*, that the claimed right warrants protection under the Due Process Clause, we need not decide whether the line of cases construing the concept of "personal dignity and autonomy" would also lend protection to the claimed right.

## III.

The question presented by the Alliance's complaint is whether the Due Process Clause protects the right of terminally ill patients to make an informed decision that may prolong life, specifically by use of potentially life-saving new drugs that the FDA has yet to approve for commercial marketing but that the FDA has determined, after Phase I clinical human trials, are safe enough for further testing on a substantial number of human beings. The Due Process Clause, as *Glucksberg* makes clear, protects those liberties "deeply rooted in this Nation's history and tradition." 521 U.S. at 721 (citation omitted). The Supreme Court has variously referred to these rights as principles "so rooted in the traditions and conscience of our people as to be

ranked as fundamental," *Snyder*, 291 U.S. at 105, and as immunities "implicit in the concept of ordered liberty," *Palko*, 302 U.S. at 325. Thus, a court's examination of our Nation's history and tradition cannot be based on so specific a description of the claimed right as would undercut the interests protected by the Due Process Clause.

**A.**

One feature of the *Glucksberg* analysis requires courts to compose a "careful description" of the asserted fundamental liberty interest before extending due process protection to it. 521 U.S. at 721. The Supreme Court has not settled on how precisely formulated the right must be. Two Justices have interpreted the "careful description" requirement as indicating that courts should identify fundamental rights at the "most specific level at which a relevant tradition protecting, or denying protection to, the asserted right can be identified." *Michael H.*, 491 U.S. at 127 n.6 (1989) (Scalia, J., with Rehnquist, C.J., concurring). Two other Justices have indicated that asserted rights not expressed at "'the most specific level' [of generality] available" can nonetheless be recognized. *Id.* at 132 (O'Connor and Kennedy, JJ., concurring). The "careful description" requirement was first invoked by the Court in *Flores*, 507 U.S. at 302 (1993), which relied on *Collins v. City of Harker Heights*, 503 U.S. 115, 125 (1992), where the notion of careful description was expressed as a pleading requirement. Since *Glucksberg*, the Court has applied this requirement once without elaboration. *See Chavez v. Martinez*, 538 U.S. 760, 775-76 (2003).

In *Hutchins v. District of Columbia*, 188 F.3d 531 (D.C. Cir. 1999), the en banc court applied the careful description requirement in its substantive due process analysis. The court viewed the careful description requirement as a means of constraining the inadvertent creation of rights that could fall

within the scope of loosely worded descriptions and thus threaten the separation of powers. *See id.* at 542-45. Despite reaching different conclusions about the appropriate level of generality in describing the claimed right, *compare id.* at 538 (citing *Michael H.*, 491 U.S. at 127 n.6 (Scalia, J., with Rehnquist, C.J., concurring), *with id.* at 555-57 (Rogers, J., dissenting) (citing *Moore,* 431 U.S. at 502-03), the court concluded that the animating principle underlying the careful description requirement is that courts should proceed with care in examining substantive due process claims. *See id.* at 538.

The Alliance's complaint contains the careful description we seek, allowing this court to consider whether the challenged FDA policy impinges upon one or more of the interests protected by the Due Process Clause. The FDA characterizes the Alliance's claimed right as a broadly stated prerogative to access post-Phase I investigational new drugs and to receive treatment, but the Alliance has defined the right more narrowly. The Alliance claims neither an unfettered right of access to all new or investigational new drugs nor a right to receive treatment from the government or at government expense. The Alliance's claim also does not challenge the Controlled Substances Act, 21 U.S.C. §§ 801 *et seq.*, or the government's authority to regulate substances deemed harmful to public health, safety, and welfare. Rather, the Alliance contends that the fundamental due process rights to privacy, liberty, and life include the right of terminally ill patients, acting on a doctor's advice, to obtain potentially life-saving medication when no alternative treatment approved by the government is available. Recognizing that the effectiveness and side effects of the investigational new drugs may still be in question after the Phase I trials have been completed, the Alliance asks only that the decision to assume these known or unknown risks be left to the terminally ill patient and not to the FDA. This description of the claimed right conforms to the demands of even the narrowest interpretation of the *Glucksberg*

**B.**

The other feature of the *Glucksberg* inquiry requires courts

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determine in the first instance whether FDA restrictions on a terminally ill patient's right of access to potentially life-saving medication that has cleared FDA Phase I trials are narrowly tailored to serve a compelling governmental interest. *See* Opinion at 30. At that time, the governmental interests will be identified by the FDA. The dissent oscillates between ignoring that this issue remains to be resolved, *see* Dissent at 9, and asserting that the issue is incapable of resolution, *see id.* at 24. Performing strict scrutiny is not a task that Article III courts have historically regarded as "impossible." *But see* Dissent at 24.

Third, the dissent suggests that the court paves the way for medicinal use of marijuana. *See* Dissent at 14, 24. There is no slippery slope from finding a right of access to potentially life-saving investigational new drugs that have cleared FDA Phase I trials for safety to finding a right of access to illegal narcotics. Marijuana is listed as a Schedule I substance under the Controlled Substances Act. A drug is included in Schedule I if it "has a high potential for abuse," "has no currently accepted medical use in treatment in the United States," and has "a lack of accepted safety for use . . . under medical supervision." 21 U.S.C. §§ 812(b)(1)(A)-(C). The investigational new drugs that have cleared FDA Phase I trials do not possess these attributes or the FDA would not be permitting their medical use in treatment, under medical supervision, by Phase II trial participants. Nothing in the court's holding supports the dissent's inference that marijuana, or any other Schedule I substance, if tested, would qualify for Phase I clearance and be potentially life-saving. By the same token, the record does not imply that a right of access exists to "federally-funded stem cell research and treatment." Dissent at 24. That issue is not before the court and the considerations that would be relevant under *Glucksberg* are not obviously similar. *See infra* n.26.

to determine whether there exists a long-standing tradition in our Nation that would protect individual access to potentially life-saving medication. Courts must focus on discerning those constitutionally protected interests whose existence can be inferred from the Due Process Clause and Supreme Court precedent construing the Clause. *See Cruzan*, 497 U.S. at 278. Although it is relevant to the substantive due process analysis that the government has never proscribed the desired conduct, this is not dispositive. The absence of regulation could be attributable to a liberty interest that is deeply rooted in this Nation's history and tradition, and therefore characterized by a history of liberty from governmental interference, but there may be another explanation. For example, a lack of regulation might indicate only that the technology of yesteryear did not warrant it.

The FDA's discussion of the merits of this question consists of a single sentence: "[The] FDA has had statutory authority to regulate drugs for almost a century, and that authority is now firmly ingrained in our understanding of the appropriate role of government." Appellee's Br. at 19.[10] We offer the following observations, mindful of the fact that the Alliance is complaining only of obstacles to post-Phase I investigational new drugs erected by the FDA and not obstacles that might be

[10] The FDA argues in its brief that the Alliance never argued in the district court that drugs were unregulated for most of our Nation's history, and thus cannot raise this argument for the first time on appeal. In fact, the Alliance argued in district court that *Glucksberg* supported its due process claim, *see* Pls.' Cross-Mot. at 8-9, and the district court relied on the *Glucksberg* analysis in dismissing the complaint. As the FDA states in its brief, whether the Alliance has asserted a fundamental right is a legal issue on which this court is fully briefed. There is no reason why the analysis cannot proceed.

erected by state consumer protection or other laws.[11]

A right of control over one's body has deep roots in the common law. The venerable commentator on the common law William Blackstone wrote that the right to "personal security" includes "a person's legal and uninterrupted enjoyment of his life, his limbs, his body, [and] his health," as well as "the preservation of a man's health from such practices as may prejudice or annoy it." WILLIAM BLACKSTONE, 1 COMMENTARIES *125, *130. This right included the right to self-defense and the right to self-preservation. "For whatever is done by a man, to save either life or member, is looked upon as done upon the highest necessity and compulsion." *Id.* at *127. As recognized throughout Anglo-American history and law, when a person is faced with death, necessity often warrants extraordinary measures not otherwise justified. Indeed the principle holds even when that action impinges upon the rights of others. *See, e.g.*, *Ploof v. Putnam*, 81 Vt. 471, 475 (1908) ("This doctrine of necessity applies with special force to the preservation of human life. . . . One may sacrifice the personal property of another to save his life or the lives of his fellows.") (internal citation omitted); *Mouse's Case*, 77 Eng. Rep. 1341, 1342 (K.B. 1609) (deciding that it is lawful to throw overboard property of another for safety of lives of passengers); RESTATEMENT (FIRST) OF TORTS § 197 (1934); *see generally* George C. Christie, *The Defense of Necessity Considered from the Legal and Moral Points of View*, 48 DUKE L. J. 975 (1996). *But see The Queen v. Dudley and Stephens*, 14 Q.B.D. 273 (1884) (holding that the defense of necessity did not justify

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[11] The FDCA does not regulate doctors in their practice of medicine; they are licensed by the states. *See Chaney v. Heckler*, 718 F.2d 1174, 1179 (D.C. Cir. 1983), *rev'd on other grounds*, *Heckler v. Chaney*, 470 U.S. 821 (1985). *See also Gonzales v. Oregon*, 126 S. Ct. 904, 922-23 (2006).

taking of innocent life). Barring a terminally ill patient from the use of a potentially life-saving treatment impinges on this right of self-preservation.

Such a bar also puts the FDA in the position of interfering with efforts that could save a terminally ill patient's life. Although the common law imposes no general duty to rescue or to preserve a life, it does create liability for interfering with such efforts. Section 326 of the Restatement (First) of Torts, first published in 1934, explained that

> [o]ne who, without a privilege to do so, intentionally prevents a third person from giving to another aid necessary to his bodily security, is liable for bodily harm caused to the other by the absence of aid which he has prevented the third person from giving.

While infrequently invoked, this common law rule is of venerable vintage. *See id.*; *see also Soldano v. O'Daniels,* 190 Cal. Rptr. 310, 313, 316-18 (Ct. App. 1983); *Miller v. Arnal Corp.*, 632 P.2d 987, 993 (Ariz. App. 1981).[12]

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[12] As the dissent notes, fundamental rights may "not [be] simply deduced from abstract concepts of personal autonomy." Dissent at 10 (quoting *Glucksber*g, 521 U.S. at 725). Were it impermissible to draw any inferences from a broader right to a narrower right, however, nearly all of the Supreme Court's substantive due process case law would be out of bounds. *See, e.g.*, *Griswold*, 381 U.S. at 484-86 (inferring specific right to use contraception from general right to be free from intrusion into "sacred precincts of marital bedrooms"); *Roe*, 410 U.S. 113 (identifying specific right to terminate a pregnancy from broader right to privacy); *Moore*, 431 U.S. at 503 (extrapolating from broader constitutional protection for "the sanctity of the family" to specific right to determine extended family living arrangements). In any event, the court's holding is not grounded in the abstract notion of personal autonomy but rather in the specific

In contrast to these ancient principles, regulation of access to new drugs has a history in this country that is of recent origin. Prior to 1906, there was essentially no drug regulation in the United States.[13] In that year Congress enacted the Pure Food and Drug Act ("1906 Act"), Pub. L. No. 59-384, 34 Stat. 768 (repealed 1938), which prohibited misbranded and adulterated foods or drugs from entering interstate commerce, 34 Stat. at 768, and prohibited false and misleading labeling, *id*. at 770.

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right to act in order to save one's own life.

[13] *See* Charles J. Walsh & Alissa Pyrich, *Rationalizing the Regulation of Prescription Drugs and Medical Devices: Perspectives on Private Certification and Tort Reform,* 48 RUTGERS L. REV. 883, 890-91 (1996); Note, *The Catch-22 for Persons with AIDS: To Have or Not To Have Easy Access to Investigational Therapies and Early Approval for New Drugs*, 69 S. CAL. L. REV. 105, 109 (1995); *see also Gonzales v. Raich,* 125 S. Ct. 2195, 2202-03 (2005). The FDA Historian Wallace F. Janssen writes that prior to 1906 was the "heyday of 'patent medicines,'" a time when "[a]nyone, no matter how ignorant or unqualified, could go into the drug manufacturing business" and when "[m]edicines . . . were sold without restriction at almost every crossroads store." Wallace F. Janssen, *Outline of the History of U.S. Drug Regulation and Labeling*, 36 FOOD DRUG COSM. L. J. 420, 422 (1981) ("*Outline of the History*"). He further recounts that in "colonial days, and long afterward, consumers . . . were their own food and drug inspectors," "there was a striking absence of statutes dealing with drugs," and, although there were food inspection laws and standards for weights and measures, *see id*. at 423, 425, "drug laws were virtually non-existent." Janssen, *America's First Food and Drug Laws,* 30 FOOD DRUG COSM. L. J. 665, 669, 671 (1975). This suggests that in this country's early history there were no restrictions on a patient's access to potentially life-saving medication, regardless of whatever restrictions may have been placed on physicians, pharmacists, apothecaries, poisons, or misbranded or adulterated substances. *See id.* at 669-72; Janssen, *Outline of the History*, at 426-28. *But cf*. Dissent at 15-17.

For a small number of particularly dangerous drugs, the 1906 Act required the labels to identify the drug's ingredients and quantities. *Id.* The statute also authorized the Bureau of Chemistry, a predecessor of the FDA, to seize nonconforming goods and to recommend federal prosecution of those who violated the 1906 Act. *Id*. at 769 § 4. The 1906 Act did not, however, limit individual access to new drugs or regulate therapeutic claims by drug manufacturers. *Cf. United States v. Johnson*, 221 U.S. 488 (1911). It thus appears that a patient still could obtain access to any new drug for medicinal use, even if the drug had no therapeutic benefit, albeit subject to the controls placed on narcotics in 1914 by the Harrison Narcotic Act. Act of Dec. 17, 1914, 38 Stat. 785.[14]

In 1938, Congress enacted the FDCA in response to the deaths of more than one hundred people, many of them children, from ingesting Elixir Sulfanilamide, which had been marketed as an antibiotic. *See* Report of the Secretary of Agriculture on Deaths Due to Elixir Sulfanilamide, S. Doc. No. 124, 75th Cong., 2d Sess. 1, 1-3 (1937) ("1937 Report").[15] For the first time, Congress required that drug manufacturers test, and the FDA review, all new drugs for safety prior to their commercial distribution. Pub. L. No. 75-717, 52 Stat. 1040 (1938) (codified as amended at 21 U.S.C. §§ 301 *et seq.*); 1937 Report at 1-3. Under the 1938 Act, a new drug could be commercially

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[14] *See generally* James L. Zelenay, Jr., *The Prescription Drug User Fee Act: Is a Faster Food and Drug Administration Always a Better Food and Drug Administration?*, 60 FOOD & DRUG L.J. 261, 263-64 (2005); Steven R. Salbu, *Regulation of Drug Treatments for HIV and AIDS: A Contractarian Model of Access,* 11 YALE J. ON REG. 401, 406-09 (1994); *cf. State of Minnesota ex rel. Whipple v. Martinson*, 256 U.S. 41, 45 (1921).

[15] *See* Salbu, *supra* note 14, at 407.

marketed only after the manufacturer filed a New Drug Application ("NDA") with the FDA that set forth medical and scientific information attesting to the drug's safety. The 1938 Act did not, however, require drug manufacturers to receive affirmative FDA approval before marketing the drug.[16] Rather, an NDA became automatically effective within a time frame set by the FDA unless the FDA determined that the drug was unsafe and barred its commercial distribution.[17] It was not until 1951, in the Durham-Humphrey Amendment, that Congress created the category of prescription drugs, i.e., drugs that are unsafe for self-medication but which can be used while under a doctor's supervision. *See* Act of Oct. 25, 1951, 65 Stat. 648 (1951) (codified at 21 U.S.C. § 353(b)).

Only in 1962 did Congress require drug manufacturers to provide empirical evidence of the effectiveness of a drug as opposed to merely the drug's safety.[18] The Kefauver-Harris Amendments, Pub. L. No. 87-781, 76 Stat. 780 (1960) (codified in scattered sections of 21 U.S.C. §§ 301-81 (1982 & Supp. IV 1986)), were enacted in response to the rash of birth defects discovered in babies whose mothers had taken Thalidomide to ease morning sickness caused by pregnancy.[19] The Kefauver-Harris Amendments transformed drug regulation and the approval process in several respects. First, the Amendments required the FDA to review a new drug for both safety and effectiveness and specified that to demonstrate effectiveness

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[16] *See* Zelenay, *supra* note 14, at 264-65.

[17] *Id*.

[18] *See* Greenberg, *supra* note 3, at 295, 300 & n.23.

[19] *See* Salbu, *supra* note 14, at 408 n.41; *see generally* HARVEY TEFF & COLIN R. MUNRO, THALIDOMIDE: THE LEGAL AFTERMATH 1-10 (1976); Janssen, *Outline of the History*, at 438.

manufacturers were required to submit data from "adequate and well-controlled investigations." 21 U.S.C. § 355(d). Second, the Amendments authorized the FDA to approve human clinical trials, regulate drug advertising, inspect drug-manufacturing facilities, and promulgate good manufacturing practices. The Amendments also required drug manufacturers to disclose to the FDA any information they received regarding the adverse consequences of approved drugs.[20] This legislation set the framework for the system of drug regulation currently in place.

Despite the increased federal scrutiny of new drugs, important aspects of patient access to drugs are unregulated by the government and appear always to have been unregulated. "The FDA's regulatory authority extends to manufacturers of drugs but not to the physicians who dispense them."[21] Thus, a doctor may prescribe a drug to a patient for a purpose other than that for which the FDA has approved the use of the drug. Such "off-label" use may occur even if the drug is not deemed safe or effective for that use. Further, it appears that the FDA has never prohibited either off-label prescription or off-label use of drugs.[22] In recent years, the FDA has been moving to permit drug manufacturers to promote the use of their drugs for off-label purposes in limited circumstances.[23] *See* Food and Drug Administration Modernization Act of 1997, Pub. L. No.

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[20] *See* Walsh & Pyrich, *supra* note 13, at 901; *see also* Zelenay, *supra* note 14, at 266.

[21] Steven R. Salbu, *Off-Use, Prescription, and Marketing of FDA-Approved Drugs: An Assessment of Legislative and Regulatory Policy*, 51 FLA. L. REV. 181, 189-92 (1999). *See Chaney*, 718 F.2d at 1180.

[22] *See* Salbu, *supra* note 21, at 189-92.

[23] *See id.* at 211.

105-115, 111 Stat. 2296 (codified in scattered sections of 21 U.S.C. §§ 301-81).

For over half of our Nation's history, then, until the enactment of the 1906 Act, a person could obtain access to any new drug without any government interference whatsoever. Even after enactment of the FDCA in 1938, Congress imposed no limitation on the commercial marketing of new drugs based upon the drugs' effectiveness. Rather, at that time, the FDA could only interrupt the sale of new drugs based on its determination that a new drug was unsafe. Government regulation of drugs premised on concern over a new drug's efficacy, as opposed to its safety, is of recent origin. And even today, a patient may use a drug for unapproved purposes even where the drug may be unsafe or ineffective for the off-label purpose. Despite the FDA's claims to the contrary, therefore, it cannot be said that government control of access to potentially life-saving medication "is now firmly ingrained in our understanding of the appropriate role of government," Appellee's Br. at 19, so as to overturn the long-standing tradition of the right of self-preservation.[24]

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[24] The court does not, as the dissent suggests, "infer[] a constitutional right to be free from regulation" from "the lack of federal regulation" in this area prior to the recent past. *See* Dissent at 14. Rather, the court infers the right from the Due Process Clause and Supreme Court precedents construing the Due Process Clause. *See supra* n. 12. The fundamental right to take action, even risky action, free from government interference, in order to save one's own life undergirds the court's decision. Our point is that the relatively short-lived history of drug regulation, particularly as regards the effectiveness of a new drug, is not, as the dissent suggests, sufficient to establish that the government has acquired title to this right by adverse possession. The same logic plainly would not serve to establish a right to recreational drugs merely because, in the grand sweep of the Nation's history, these regulations are of relatively recent

**C.**

The Alliance's claim also falls squarely within the realm of rights the Supreme Court has held are "implicit in the concept of ordered liberty." *Palko*, 302 U.S. at 325. Specifically, the claimed right is implied by the Court's conclusion in *Cruzan* that due process protects a person's right to refuse life-sustaining treatment. *See Cruzan*, 497 U.S. at 279. Writing for the Court, Chief Justice Rehnquist noted in examining the origins of the doctrine of informed consent that the Court had observed early on that "[n]o right is held more sacred, or is more carefully guarded, by the common law, than the right of every individual to the possession and control of his own person, free from all restraint or interference of others, unless by clear and unquestionable authority of law." *Id*. at 269 (quoting *Union Pacific R. Co. v. Botsford*, 141 U.S. 250, 251 (1891)). The Court reasoned that "[t]he logical corollary of the doctrine of informed consent is that the patient generally possesses the right not to consent, that is, to refuse treatment." *Id*. at 270. Confronting for the first time what it described as a "perplexing question with unusually strong moral and ethical overtones," *id*. at 277, the Court turned to the language of the Fourteenth Amendment and its precedent to determine whether "the United States Constitution grants what is in common parlance referred to as a 'right to die,'" *id*. The Court reasoned that "[t]he principle that a competent person has a constitutionally protected liberty interest in refusing unwanted medical treatment may be inferred from our prior decisions." *Id.* Without qualification, the Court stated: "It cannot be disputed that the Due Process Clause protects an interest in life as well as an interest in refusing life-sustaining medical treatment." *Id.* at 281.

A similar analysis leads to the conclusion that the Due

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vintage.

Process Clause protects the liberty interest claimed by the Alliance for its terminally ill members. *See supra* Part III.A. The text of the Due Process Clause refers to protecting "liberty" and "life." Although there is no similarly clear textual basis for a "right to die" or refusing life-sustaining medical treatment, the Supreme Court in *Cruzan* recognized, in light of the common law and constitutionally protected liberty interests based on the inviolability of one's body, that an individual has a due process right to make an informed decision to engage in conduct, by withdrawing treatment, that will cause one's death.[25] The logical corollary is that an individual must also be free to decide for herself whether to assume any known or unknown risks of taking a medication that might prolong her life.

Like the right claimed in *Cruzan*, the right claimed by the Alliance to be free of FDA imposition does not involve treatment by the government or a government subsidy. Rather, much as the guardians of the comatose patient in *Cruzan* did, the Alliance seeks to have the government step aside by changing its policy so the individual right of self-determination is not violated. The Alliance claims that there is a protected right of terminally ill patients to choose to use potentially life-saving investigational new drugs that have successfully cleared Phase I. If there is a protected liberty interest in self-determination that includes a right to refuse life-sustaining treatment, even though this will hasten death, then the same liberty interest must

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[25] It was only in the course of balancing an individual's liberty interest against the relevant government interests that the Court indicated "the dramatic consequences involved in the refusal of [life-sustaining] treatment would inform the inquiry as to whether the deprivation of that interest is constitutionally permissible." *Cruzan*, 497 U.S. at 279. The Court's holding allowed the government to protect the autonomous exercise of the right to refuse life-sustaining treatment; it did not undermine the right.

include the complementary right of access to potentially life-sustaining medication, in light of the explicit protection accorded "life."[26] Our reasoning is not unlike that of the Supreme Court in *Eisenstadt*, 405 U.S. 438, where the Court held that the right to be free from unwanted government intrusion into the fundamental decision whether to have children establishes a right of access to contraception.

Contrary to the FDA's position, nothing in this court's precedent or that of the other circuit courts of appeal conflicts with our analysis. Although the district court concluded, in reliance upon our decision in *Dronenberg*, 741 F.2d at 1396, that lower courts may not consider claims to new substantive due process rights and principles not previously identified by the

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[26] The dissent fails to see how the court can reason from a right to refuse life-saving treatment to a right of access to life-saving treatment, *see* Dissent at 17-18, but the two go hand in hand. In either instance — refusal or access — the key is the patient's right to make her own decision free from government interference. Moreover, the right of access to investigational new drugs that have cleared Phase I trials is different from and does not imply a general right to receive life-saving treatment, as the dissent, Dissent at 24, and the district court presumed. Nor does the court reach the question whether there is such a right for that is not the Alliance's claim.

Finally, the dissent mistakenly suggests the court offends the "concept of ordered liberty" because the court's decision is "contrary to the expressed will of Congress and the Executive and to the deference courts owe to the democratic branches on such controversial matters." Dissent at 22-23. Although the term "ordered liberty" necessarily remains somewhat unclear, it cannot stand for a broad principle of deference to the political branches whenever "unknown questions of science" are involved. *See id*. Otherwise, it would establish a zone in which the political branches would be free to regulate persons unconstrained by the individual liberties preserved in the Constitution.

Supreme Court, *see supra* page 9, this court has addressed substantive due process claims on a number of occasions. *See, e.g.*, *N.Y. State Opthalmological Soc'y v. Bowen*, 854 F.2d 1379 (D.C. Cir. 1988). Most pertinently, in *Butera v. District of Columbia*, 235 F.3d 637 (D.C. Cir. 2001), the court confronted, in the context of a qualified immunity defense, the claim of a substantive due process right to life, personal security, and bodily integrity. *Butera* involved a suit under 42 U.S.C. § 1983 brought by the mother of a man who was shot while working undercover for the police department. The court in *Butera* did not suggest that the advisory admonition in *Dronenberg*, 741 F.2d at 1396, precluded either the substantive due process inquiry or the conclusion that a fundamental right was implicated.

The decisions in the other circuits on which the FDA relies likewise fail to support its position that there is no substantive due process right of access to potentially life-saving treatment. *United States v. Burzynksi Cancer Research Institute*, 819 F.2d 1301 (5th Cir. 1987), which held that the doctor and patient had not stated a constitutional tort based on the allegedly improper seizure of the doctor's patient records and thus that they did not overcome the defendant's claim of qualified immunity, *id.* at 1310-11, bears no legal or factual relevance to the question before this court. The statement in *Carnohan v. United States,* 616 F.2d 1120, 1122 (9th Cir. 1980), that "[c]onstitutional rights of privacy and personal liberty do not give individuals the right to obtain [the cancer drug] laetrile free of the lawful exercise of government police power," was dictum; the Ninth Circuit never reached the merits of the claimed fundamental right of access as the complaint was dismissed for failure to exhaust administrative remedies.

Further, as the Alliance pointed out in its brief, the terminally ill patients in *Rutherford v. United States*, 616 F.2d

455 (10th Cir. 1980), like those in *Carnohan*, sought access to laetrile, a new cancer drug that had not cleared FDA's Phase I safety hurdle and thus had not been approved for expanded testing on humans in ongoing clinical trials, *see id.* at 456-57. The Tenth Circuit rejected a right to laetrile, reasoning that the choice of a particular treatment or medication is "within the area of governmental interest in protecting public health." *Id.* at 457. Of course, the government's interest in regulating has no bearing upon the identification of a fundamental right. Rather, its interest is to be considered only if, and after, a court recognizes a fundamental right; at that point, the burden shifts to the government to demonstrate a narrowly tailored "compelling interest" in burdening that right. Because the FDA had neither eliminated the possibility that laetrile was a poison nor approved the drug for basic human testing in Phase I trials, the government's interest in *Rutherford* might well have been sufficiently compelling to warrant restricting access to the drug. In this case, the government's interest may prove to be weaker because the Alliance seeks only access to investigational new drugs that the FDA, after Phase I human trials, has deemed sufficiently safe for human testing on a substantial number of human beings. In other words, the Alliance seeks for its members the same right of access enjoyed by those terminally ill patients lucky enough to secure a spot in Phase II trials.

Accordingly, we hold that the district court erred in dismissing the Alliance's complaint pursuant to Rule 12(b)(6) for failure to state a claim. We conclude, upon applying the *Glucksberg* analysis and heeding the protected liberty interests articulated by the Supreme Court, that where there are no alternative government-approved treatment options, a terminally ill, mentally competent adult patient's informed access to potentially life-saving investigational new drugs determined by the FDA after Phase I trials to be sufficiently safe for expanded human trials warrants protection under the Due Process Clause.

The prerogative asserted by the FDA — to prevent a terminally ill patient from using potentially life-saving medication to which those in Phase II clinical trials have access — thus impinges upon an individual liberty deeply rooted in our Nation's history and tradition of self-preservation. *See Glucksberg*, 521 U.S. at 721; *Flores*, 506 U.S. at 302. The district court never reached the question of whether the challenged FDA policy violates this protected liberty interest, and we therefore remand the case to the district court to determine whether the FDA's policy barring access to post-Phase I investigational new drugs by terminally ill patients is narrowly tailored to serve a compelling governmental interest.

# Attachment C

Drug Czars

Editorial in the Wall Street Journal
By Steven Walker

May 7, 2007

THE WALL STREET JOURNAL. ONLINE



May 4, 2007

COMMENTARY

# Drug Czars

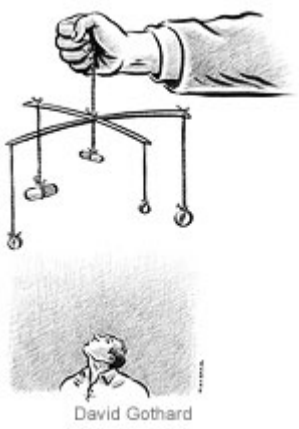
By STEVEN WALKER
*May 4, 2007; Page A15*



The Food and Drug Administration recently argued in the D.C. Court of Appeals that it has the power to ban meat and vegetables without violating anyone's fundamental rights. The agency chose this bizarre position in an attempt to counter arguments made by patients and their advocates in *Abigail Alliance v. von Eschenbach*. This groundbreaking case challenges the agency's refusal to grant access to investigational drugs, even as a last resort for terminally ill patients.

Last year, a three-judge panel decided that the FDA is violating the due- process rights of terminally ill patients by denying them access to promising investigational drugs. In response the FDA moved for a rehearing by the full court, hoping to prevent a lower court-supervised examination of whether its draconian policies actually serve a narrowly tailored compelling governmental interest. In layman's terms, this means the FDA would have to show its policies toward terminal patients are so critical to the well-being of society that they supersede (in broad and highly imperfect fashion) the fundamental right of an individual to pursue life free of undue government interference. The FDA knows their policies will not survive this test, and doesn't want the question asked.

Consider the FDA's handling of Genasense, a new drug for melanoma and chronic lymphocytic leukemia (CLL), two often terminal forms of cancer. The drug is being developed by Genta, a small, innovative company with only one approved drug and limited financial resources. Despite compelling evidence that Genasense is making progress in fighting both diseases, the FDA appears determined to kill the drug.




In the case of the melanoma application, instead of reviewing the clinical-trial data in accordance with usual methods (which showed positive results), the FDA chose a nonstandard statistical approach aimed at discrediting the results. The agency used this analysis in its briefing to its advisory committee, claiming that the drug might not be effective. The committee then relied on that information to vote against approval.

Now, Genta has found a serious mathematical error in the FDA's analysis, rendering its results meaningless. Genta is filing a complaint under the Federal Data Quality Act to correct the record. But in the meantime, the drug remains unapproved and melanoma patients continue to wait.

Genasense was also shown in a well-run, randomized clinical trial (the FDA's gold standard) to cause a complete disappearance of disease in 17% of patients with advanced CLL when combined with two older drugs. Just 7% of patients in a control group who received only the older drugs experienced similar benefit. The responders to Genasense have seen their relief last an average of 36 months, while those using other drugs saw their cancer return, on average, in 22 months.

Following these results, the Director of the FDA's cancer division, Dr. Richard Pazdur, again convened a public meeting of his advisory committee. After an agency presentation designed to elicit a negative outcome, the panel voted 7 to 3 against approval, triggering an immediate reaction of surprise and dismay among many CLL experts.

But the committee vote is less surprising if one knows that the FDA appointed several voting consultants to the committee (none of them CLL experts), and recused from the meeting the only sitting member of the committee who is an expert in CLL. Perhaps even more troubling, two of the voting committee members worked behind the scenes as undisclosed consultants for the FDA on Genasense, then without disclosure voted in the open meeting.

A shocked Genta quickly requested a meeting with the FDA to seek clarity on the agency's position, and to present additional information from patient follow-up. On the referral of an eminent leukemia expert, Genta asked if we would attend the meeting as witnesses in our capacity as patient advocates. No compensation was offered, requested or received.

Most of the meeting was consumed by getting the FDA to admit the obvious: The long-lasting, complete disappearance of CLL and its symptoms constituted "clinical benefit." Making these arguments were two cancer-medicine professors at M.D. Anderson Cancer Center, the recused ODAC member and an immediate past president of the American Society of Hematology -- all experts in CLL. None were employees of Genta and collectively represented a far more qualified advisory committee than the one that the FDA had convened.

The FDA's inane answer to the CLL experts was that the long-lasting disappearance of disease in patients taking Genasense was a "theoretical construct" and not grounds for approval.

The experts explained to the FDA that complete responses in advanced CLL patients are the medical equivalent of the Holy Grail. The FDA finally agreed, but was unimpressed with emerging data showing responders to Genasense living longer than responders in the control group.

The experts were unanimous in advising that Genasense should be approved, but the FDA was unmoved. The agency's Dr. Pazdur suggested that Genta could make the drug available as an unapproved treatment through an expanded access program -- this from a regulator fond of stating that the best way to get a drug to patients in need is through approval! In this case the agency was saying to Genta: We are not going to approve your drug, but any patient who needs it can have it so long as you give it away.

Genta responded that nonapproval would be a denial of patient access to Genasense because they could not afford to give it away in an expanded access program. Twice, Dr. Pazdur referred to that logic as a "business decision."

Less than 48 hours later, the FDA rejected Genasense. Within days Genta made a "business decision," laying off a third of its staff in a cost cutting move aimed at keeping the doors open long enough to appeal the FDA's decision. The appeal was filed in early April. Genta's announcement of the filing included a statement from one of the expert physicians: "It is puzzling that they would deny approval to a drug that met its primary and key secondary endpoint,

especially since these findings were observed in the only randomized controlled trial that has ever been conducted in patients with relapsed CLL."

The FDA's handling of Genasense lays bare the all too common, aggressive incompetence of the FDA's cancer-drug division and should lead to an immediate examination of its policies and leadership, followed by swift corrective action.

As for the FDA's belief that their power to control us and even deny us the pursuit of life itself is unlimited under the Constitution, we can only hope the appeals court disagrees. An agency that blocks progress against deadly diseases -- while arguing that its power to do so is above challenge -- is in dire need of a court supervised review.

***Mr. Walker is co-founder and chief adviser for the Abigail Alliance for Better Access to Developmental Drugs . He receives no compensation for his work as an advocate, nor has he ever received compensation from any private or public-sector entity involved in drug development, approval or marketing.***

**URL for this article:**
http://online.wsj.com/article/SB117824324837591782.html

# Attachment D

ODAC and the FDA, Arms-Length or Arm-In-Arm?

Slides from Presentation to the Oncologic Drugs Advisory Committee
by Steven Walker

September 6, 2006

Abigail Alliance
for Better Access to Developmental Drugs

**Oncologic Drugs Advisory Committee**
**September 6, 2006**

## ODAC and the FDA
## Arms-Length or Arm-In-Arm?

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**Oncologic Drugs Advisory Committee**
**September 6, 2006**

**Does the Office of Oncology Drug Products Have Too Much Control Over ODAC?**

**Is ODAC Too Close to the Office of Oncology Drug Products?**

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**Oncologic Drugs Advisory Committee**
**September 6, 2006**

**How Are ODAC Members Selected and Who Selects Them?**

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ODAC Member Selection

- The Nomination Process - Transparent
- **The Screening Process - Murky**
- **The Selection Process - Opaque**

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ODAC Member Selection

Final Selection – How It Is Done

- Nominations are Sent to the Division
- The Division Decides Who They Want
- And Who They Don't Want

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Technical ODAC Members
Where Do They Come From?

Who Is "The Division?"

**"The Division" is the Office of Oncology Drug Products**

## A Memorandum

Memorandum

Date:
To:
From: Richard Pazdur, M.D., Office Director
Office of Oncology Drug Products
Subject: Nomination for Oncologic Drugs Advisory Committee

Dear:

Thank you for your interest in the Oncologic Drugs Advisory Committee (ODAC) at the Food and Drug Administration, Center for Drug Evaluation, Office of Oncology Drug Products. After careful consideration, I am sorry to inform you that the vacancy for membership on this committee has been offered to, and accepted by another nominee.

The agency was very fortunate to receive a large number of extremely qualified and highly respected recommendations, you being among them. However, with such a varied and promising field of nominees, and after much deliberation, the candidates were chosen based not only on their qualifications but on the needs of the committee with consideration to issues and products inherent to the applications and processes of the agency.

Again, thank you for your interest in the ODAC.

Best,

Richard Pazdur, M.D.
Director
Office of Oncology Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration

## The Division and ODAC

### What Else Does the Division Control

- When to Convene the Committee
- The Subjects/Drugs to be Discussed
- Content/Spin of FDA Briefing Documents

## The Division and ODAC

### More Division Control

- Who Sits and Votes As Members
- Who Sits and Votes as Consultants
- What Questions are Posed for a Vote

## The Law

Federal Advisory Committee Act (FACA)

- the advisory committee will not be inappropriately influenced by the appointing authority or by any special interest, but will instead be the result of the advisory committee's independent judgment;"

## The Regulation

Title 21 Code of Federal Regulations Subchapter A - Part 14

- "An advisory committee is utilized to conduct public hearings on matters of importance that come before FDA..."
- Voting members serve as individuals and not as representatives of any group or organization which nominated them or with which they may be affiliated.
- Its membership is balanced fairly in terms of the points of view represented in light of the functions to be performed.
- It is constituted and utilizes procedures designed to assure that its advice and recommendations are the result of the advisory committee's independent judgment.

## Clear Intent of the Law and Regulation

**The Purpose of an FDA Advisory Committee**

**is to Provide Balanced, Independent Advice**

**In A Manner Open to the Public**

## An Important Question

Should the Office of Oncology Drug Products Control the Membership of ODAC?

**Does This Practice Compromise the Independence Of ODAC?**

## An Important Question

**Is ODAC Too Close to the Office of Oncology Drug Products?**

## Oncologic Drugs Advisory Committee
June 2, 2006

Last ODAC Meeting – More Evidence of Arm-in-Arm Relationship

Director's Comments Regarding Service of Departing Members

Dr. Silvana Martino, D.O., Chair
Dr. Bruce Cheson, M.D.
Dr. Gregory Reamon, M.D.

## Oncologic Drugs Advisory Committee
June 2, 2006
Statement by Dr. Richard Pazdur

Regarding all three departing members:

"...we have really used them quite extensively, and they have developed I think very close working relationships with many at the FDA."

## Oncologic Drugs Advisory Committee
June 2, 2006
Statement by Dr. Richard Pazdur

[Dr. Martino] "...has always been available to the FDA staff to provide consultations to us and to bounce off ideas in a very professional and positive manner."

## Oncologic Drugs Advisory Committee
June 2, 2006
Statement by Dr. Richard Pazdur

Dr. Cheson .... "has provided to the Agency numerous consultations outside of the ODAC meetings on end of phase two meetings and official and unofficial consultations with the members of the staff."

Oncologic Drugs Advisory Committee
June 2, 2006
Statement by Dr. Richard Pazdur

[Dr. Reamon] ... "has been available, again like the other members of this committee, in helping us with end of phase two meetings, difficult questions that we have regarding exclusivity, and other pediatric issues that the Agency faces."

**How Involved are ODAC Members with FDA**

**Questions That Deserve Answers**

- Are members of ODAC working directly with FDA on regulatory strategies for specific INDs Outside the Public Meeting Process?
- Do ODAC members work with FDA on active INDs prior to scheduling of meetings on an NDA or BLA for those drugs?
- Do they assist with or attend end of Phase II meetings for specific drugs at the request of the FDA?
- Have any of the drugs they worked on with FDA been later brought before ODAC for its advice?

## Potential Conflict of Interest 1

How Can a Committee Provide Balanced, Outside, Independent Advice to FDA If The Committee Roster and Agenda are Entirely Controlled by the FDA Staff Asking for That Advice

## Potential Conflict of Interest 2

How Can any Member, or the Committee as a Whole, Provide Outside Independent Advice to FDA?

If Some or All of the Members Also Work Out of the Public View Directly With FDA to Set Agency Policy or Strategies Regarding INDs That May Eventually Come Before the Committee?

## Procedural Problems

Deliberations of Advisory Committees Are by Law and Regulation to be Open to the Public

How Do Formal and Informal Consultations With FDA Staff by ODAC Members Outside the Public Meeting Process Meet This Standard?

## The Law and Regulation Are Clear

The ODAC is Not Supposed to Be a Part of, An Extension of, or a Tool of the Office of Oncology Drug Products

ODAC Is Intended to Advise and Instruct the Office from a Vantage Point that is Clearly Outside and Independent of the FDA in a Manner Openly Visible to the Public

## A Balanced, Independent, Public ODAC How Do We Get There?

- Remove Any and All Nomination and Selection Tasks for ODAC Members and Other Voting Members from the Office of Oncology Drug Products and Probably from CDER
- Require That All Nominations to ODAC Be a Matter of Public Record – Including Identification of Both the Nominating and Nominated Parties
- Limit All Interactions Between FDA and ODAC Committee Members to the Open Committee Meeting Process or to the Formal Assignment Process Specified by Regulation

## A Balanced, Independent, Public ODAC How Do We Get There?

- End Non-Public ODAC Member Participation in FDA Internal Proceedings Regarding Active INDs, Such as End of Phase II Meetings
- Post All Pending Committee Vacancies No Less Than Six Months Prior to the Vacancy Opening Up on the FDA's Advisory Committee Web Page
- Make the Advisory Committee Member Selection Process and Duties More Transparent - Immediately Post the Necessary Information on the Agency's Web Site

## An Independent ODAC Closing Thoughts

The Role of This Committee is to Provide Outside, Balanced, Independent Advice To FDA on Matters of Critical Importance to The Cancer Research, Clinical and Patient Community

The Member Selection Process, Administration and Utilization of Advisory Committees by FDA Should Be Reformed to Ensure that the Intended Balance, Independence and Transparency to the Public is Achieved

Abigail Alliance
for Better Access to Developmental Drugs

Working for Patients

# Attachment E

Making FDA Work for Patients

By Steven Walker

Legal Backgrounder, Vol. 20, No. 10.
Washington Legal Foundation.

February 25, 2005

Legal Backgrounder

WLF Washington Legal Foundation

Advocate for freedom and justice®
2009 Massachusetts Avenue, NW
Washington, DC 20036
202.588.0302

Vol. 20 No. 10 February 25, 2005

# MAKING FDA WORK FOR PATIENTS

by

Steven Walker

As a nation, we are accustomed to scientific progress. The advances of the last century have, for example, allowed us to live years longer in better health, and brought us new medical treatments that can cure or control a variety of previously limiting or fatal diseases.

Now, during this period of unprecedented success, patients face a regulatory crisis of massive proportions. Our regulatory system has failed to evolve with the advancing science, leaving us with a drug development and approval process no longer capable of effectively protecting and promoting the public health. At the center of this crisis is the U.S. Food and Drug Administration (FDA).

A vast number of patients are being left out of medical progress — progress inhibited by a federal agency which tells dying patients that waiting, and dying while they wait, is in their best interests.

***Background***. In the 1970s, the United States made a national commitment to basic medical research and has steadily increased funding for those efforts through the present. Over the last 25 years, federal policy has also recognized the potential of the private sector to accelerate medical progress by utilizing its capital and efficient product development models to tackle the most difficult part of the process: transforming basic research discoveries into usable treatments. In the 1980s and 1990s, in an effort to boost industry and investor interest, Congress passed a series of laws creating incentives for private-sector investment in development of new and better treatments.

This focus on basic research and engaging the private sector is now paying off. New information regarding causes and possible treatments for a variety of serious diseases is emerging from our basic research laboratories into the hands of public- and private-sector organizations that can transform such knowledge into safe and effective new treatments.

In the meantime, the FDA has been relying on a drug development and approval model conceived decades ago. In the early 1960s, realizing that science does not always succeed, and that pharmaceutical companies and physicians are fallible, Congress modified the Food, Drug and Cosmetic Act to require the FDA to determine that new medicines are both safe *and* "effective." Until then, the FDA had long been regulating drug safety, but had no mandate to evaluate effectiveness.

At that time, biomedical knowledge and the technology needed to broaden it were crude by today's standards. Drug discovery proceeded largely by trial and error, screening thousands of compounds to find a few that worked in a lab, and perhaps one that eventually could serve as a viable treatment. Researchers were flying blind. The state of the art also limited the options available to the FDA, leaving the regulators with no choice but to devise equally primitive methods for measuring effectiveness.

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**Steven Walker** is Regulatory Advisor to the Abigail Alliance for Better Access to Developmental Drugs, an Arlington, Virginia-based patient group dedicated to helping cancer patients and others with life-threatening and serious diseases.

The basic elements of our comparative clinical trials system are fourfold. Researchers first determine (using a small number of volunteers) an appropriate dose and whether the drug appears to be safe at that dose (i.e., substantially less dangerous than the condition it was intended to treat). Next, the drug is tested in a larger number of patients with the specified condition. It is then given to an even larger number of people with the condition and compared to a similar number of people with the same condition, called controls. Control group patients might receive nothing, a placebo (sugar pill), or an already-approved drug known to work at some level for the same condition. Finally, the outcomes for the two groups are compared and the results are used to evaluate whether the new drug is more effective than nothing, or at least is as effective as an older drug. If it is found to be acceptably safe and works at some level based on these standards, also called endpoints, the FDA may approve it.

The data produced from the clinical trials are well suited to evaluation using the mathematical tool of statistics, and FDA adopted the rules of statistics from the outset as the basic drivers for clinical trial design and analysis of trial results. The thinking was to structure the trials in such a way that the data produced would be amenable to statistical analysis and would meet its theoretical tests for validity. As the field of human clinical testing evolved, the trials were increasingly designed to facilitate the strengths and also the severe limitations of statistical analytical techniques. Simultaneously, the FDA established increasingly detailed and rigid standards governing approval decisions for new treatments. These standards were largely statistical in nature, hinging on artificial measures of data validity called "probability values" and "confidence limits." Another requirement of the statistical approach was the need to compare "apples to apples" in the clinical trials, resulting in the parsing of a single disease (*e.g.*, colon cancer) into many disease sub-types for which an isolated approval could be obtained.

On the positive side, this approach did not require the FDA to know for certain what caused the disease being treated or what the new drug was doing to treat it. In other words, it enabled the FDA to be "science-blind." In a time when those things were often unknowable, a phased clinical trials system would still allow the FDA to achieve its mission of protecting and promoting the public health. Another plus for regulators was that because the statistical approach did not require any detailed scientific knowledge or clinical skills, decision-making based on sound scientific and clinical judgment was not required or even allowed. The removal of these factors from the approval process relieved decision-makers at the FDA from any direct accountability for approving a drug that later proved to be unsafe, or for delaying approval of a new treatment that could have saved many lives.

On the negative side, the FDA's focus on fine points of statistical methodology in making approval decisions for new treatments caused the trials to be designed with restrictive entry criteria that excluded many patients from participation. Perhaps the most damaging effect of the focus on statistical methodology was that it often had the effect of banishing from the approval process consideration of the real science underlying the disease and the drug.

The science-blind approach to drug assessment has also fostered a risk-averse culture at the FDA, one strongly favoring the invisible mistake of delaying the approval of safe and effective treatments to minimize the chance of making a highly visible mistake — approving an unsafe or ineffective drug that must later be withdrawn. The way the FDA is organized has reinforced this risk aversion. It is an organizational structure where responsibility for decisions and performance is spread thin and wide across a number of disciplines and offices. This structure provides little incentive for any one reviewer to step outside his or her own chute of responsibility into the path of accountability. When mistakes happen, the agency invokes a rote defense — procedures and policies were followed, statistical standards were met, and therefore the mistake was unavoidable. No one individual is responsible because no one individual can be responsible.

***The Effect***. The process of moving new discoveries from the laboratory to the bedside is called "translation," and there is widespread agreement that we are failing to convert an unprecedented expansion of scientific knowledge into more effective treatments. There is considerably less agreement on why we are failing, mainly caused by a near cult-like belief in the purity of statistical methodology in the drug approval



ISBN 1056 3059

process. In this new age of "smart science" drug invention, we are haltingly laboring ahead with a decades-old science-blind translation system.

The FDA has worked diligently to preserve and entrench its primitive methods, even as the field it regulates surpasses it. Had the FDA kept pace, we would now be evaluating and approving some new drugs and treatments based on our knowledge of the causes of disease, and direct observation of how a new drug affects the cause. We would be using science-based facts obtained from direct observation with small, scientifically-driven clinical trials designed to confirm reasonable safety and effectiveness rather than to establish it, and we would follow up after approval of a new treatment with long-term monitoring in actual patient populations.

Unfortunately, the FDA claims to have no idea how to do this and has begun well-intentioned but unfunded initiatives called "Critical Path" and "Stimulating Innovation" to try to figure it out. In typical fashion, the agency has reviewed its practices and the field in general, and concluded that most of the problems lie beyond its walls. Until the FDA realizes that the organizations outside the FDA are simply responding to its mandates, sponsors trying to translate discoveries to patients will have to make do with the FDA's science-blind approach.

***The Patients***. As the FDA continues to stand still, encumbered with a bureaucratic resistance to change, it remains a drag on medical progress and a lethal barrier to a vast number of terminally-ill Americans trying to gain access to that progress. Those patients invariably find themselves fighting two adversaries: their life-threatening disease and the FDA's "process before patients" system in which serving the best interests of patients is secondary to the FDA's inflexible policies and practices.

Every year more than one-half million Americans die in the U.S from cancer alone. As recently as ten years ago, there was little to be done. The pipeline of new cancer drugs showing evidence of effectiveness was sparsely filled. The focus of most clinical trials was to find new ways to use a small number of existing drugs already known to be inadequate, and progress was being made in rare, tiny steps. According to experts, cures were many decades away.

By the mid-1990s, however, a first wave of knowledge-based, smart science cancer drugs were entering the FDA's clinical trials process, with many more in pre-clinical development. That number has now grown to several hundred highly-innovative investigational treatments in clinical trials today. The new drugs are variable in their genesis and design, reflecting the diverse nature of scientific advances. In cancer, they consist of small chemicals designed to block receptors on cancer cells, manufactured biological antibodies designed to gum up cancer cell signaling mechanisms, and even biological molecules attached to small radioactive particles that are injected into the bloodstream where they seek out cancer cells and deliver the radiation directly to the tumors. Some show startling evidence of safety and effectiveness in early testing, but take years to reach patients as they travel the tortuous path of the FDA's outmoded drug development and approval system.

One of these new creations, and its path to patients, provides a telling example of the problem. A drug called STI-571 (now known as Gleevec) worked so well for patients in a small Phase I trial, many labeled it a new miracle cancer drug. In 1998, all 31 patients in the trial experienced dramatic positive responses to the drug without any serious side-effects. Tragically, instead of being delivered immediately to patients with a highly-lethal form of leukemia, the FDA required a Phase II trial as a matter of pro-forma policy before the drug could be made available to anyone outside a clinical trial. Some patients eventually got the drug before it was approved based on data collected in the Phase II trial and a program known as "compassionate use." Many patients, however, died waiting for the FDA to approve Gleevec; an approval that didn't come for more than two years after its safety and efficacy were well established. It has since proven to be effective in treating at least one additional form of lethal cancer, and other life-saving and life-extending uses for the drug appear likely to emerge.



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Thanks to the ineffectiveness of FDA policies governing clinical trials and approval standards, the Gleevec scenario has repeated itself numerous times in the last seven years where drugs have been discovered to be safe and effective against a variety of deadly cancers shown in early and even late-stage clinical trials. The FDA's staunch resistance to change has led to slowed and even stalled progress against cancer and other deadly diseases, and a mounting toll of shortened lives that may now number in the millions.

Despite the obvious and increasing collision between scientific progress and the FDA's failure to keep up, the agency has yet to implement a single change resulting in direct benefit to patients, opting instead to begin studies and initiatives that will take years to yield results. In the meantime, its forty-year-old assessment process remains in place, and a vast number of patients die every year waiting for medical progress already made to reach them.

The recently reported safety problems with pediatric anti-depressant drugs and with the pain reliever Vioxx arose from the same fundamental shortcomings that cause the FDA to routinely delay approvals for breakthrough cancer treatments.

Simply put, statistics is a set of powerful mathematical tools scientists use to help them test or understand data from their experiments, but statistics are almost never used as the *only* basis for making decisions. Statistical methods alone give a limited view of scientific data when they lack an understanding of the underlying scientific phenomena. Yet the FDA has built its entire system of drug development and approval around just that approach. The result is an FDA operating with outdated, ineffective regulations and policies that drive up the cost of medical progress and prevent the delivery of that progress to those who need it most: patients suffering from serious and terminal diseases. The agency needs new decision-making tools and approval authorities that are based on real science, not just statistical measures like "p-values" and "confidence limits." If you don't know what a p-value or confidence limit is, you just might be better at recognizing and approving new breakthrough cancer drugs than the FDA, saving a lot of lives as a result.

***Possible Solutions***. The Abigail Alliance for Better Access to Developmental Drugs and its counsel, the Washington Legal Foundation, have proposed a regulatory reform called "Tier 1 Initial Approval." It is designed to make promising new treatments available to terminally-ill patients in a time frame meaningful to them — that is, while they are still alive. The program would allow drug sponsors to sell an investigational drug (a drug undergoing clinical trials in humans) to patients with life-threatening illnesses who have not been able to gain entry into a clinical trial. Those patients would thus have an opportunity to take the same risks, and seek the same potential benefits, as patients in the clinical trials. Tier 1 is a comprehensive proposal intended to improve patient access to medical progress while protecting the clinical trials system, providing incentives for sponsor participation, and creating a potential for insurance coverage and patient assistance programs to cover the cost of Tier 1 drugs for patients reasonably choosing to pursue better, longer lives. A petition asking for adoption of the new authority was submitted to the FDA on June 11, 2003. The petition shows in detail that such a program is within the FDA's statutory authority and does not require new legislation.

On July 28, 2003, the Abigail Alliance and the Washington Legal Foundation filed a lawsuit in federal court against the FDA and its parent agency, the U.S. Department of Health and Human Services, asking for a ruling that the FDA's policies violate the constitutional rights of terminally ill patients with no approved treatment options by depriving them of life and liberty without due process and by infringing on their right to privacy. The U.S. District Court for the District of Columbia rejected these constitutional arguments in an August 30, 2004 ruling, and the case is now on appeal.

Ultimately, the remedy for overcoming the regulatory barriers between promising new medicines and the dying patients who desire them rests with a cultural change within FDA: a perspective in which the agency considers itself at fault when it makes a mistake in delaying an important new medicine no less than when it makes a mistake in approving a new medicine. How to bring this cultural shift about is the major challenge facing lawmakers and agency leaders.



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# Attachment F

Decelerated Approval

Presentation to the Oncologic Drugs Advisory Committee
By Steven Walker

November 8, 2005

**Presentation to the Oncologic Drugs Advisory Committee**
**November 8, 2005**

**By**

**Steven Walker**
**Abigail Alliance for Better Access to Developmental Drugs**

# Decelerated Approval

My name is Steven Walker. I am Chief Advisor to the Abigail Alliance for Better Access to Developmental Drugs. I am a volunteer and receive no compensation of any kind for my efforts as a patient advocate or for my work on behalf of the Abigail Alliance. I am paying my own expenses to be here today, and I have no financial relationships with drug companies or any other entity or organization directly involved in the development, approval or sale of medical treatments.

**Slide 1**

**The FDA's Decelerated Approval Initiative for New Cancer Drugs**

I suspect many of you were here for the first ODAC meeting on this subject in March 2003. Frank Burroughs, President of the Abigail Alliance, and I were here as well, and we spoke at that meeting asking that the FDA not proceed with the policies they were clearly about to launch. In my opinion, the FDA wasn't really looking for ODAC's advice on its plans, but rather used the meeting as a platform to roll out what can only be described as a decelerated approval initiative.

The FDA also should have known - and in fact it is hard to believe that they did not know - that its decelerated approval initiative would be devastating for terminally ill cancer patients whose only hope was gaining access to medical progress while still alive.

Despite the stark truth of what the FDA's new policies would do in slowing translation of new therapies to the clinic and the patients that needed them to live, the FDA forged ahead – rolling out its plans to turn accelerated approval and Phase IV clinical trials into a high risk minefield for sponsors. In fact, on that day in March 2003, the FDA effectively eliminated the accelerated approval pathway as a viable mechanism - the exact opposite of what the FDA should have been doing in this time of accelerating scientific progress against cancer.

I would now like to take you through the start and evolution of the FDA's decelerated approval initiative. I am going to read to you some of the statements made by FDA in ODAC meetings to launch the decelerated approval initiative, then talk about a couple of

examples that illustrate the effect those policies have had on the effectiveness and ethics of our clinical trials and translation system.

At the start of the March 12, 2003 meeting, Dr. Richard Pazdur concisely outlined the FDA's new policies regarding accelerated approval. Dr. Pazdur opened with the following comment:

**Slide 2**

"Accelerated approvals have been granted with the trial design using single arm trials in refractory populations as stated previously. These trials obviously allow more rapid trial completion and hence expedite drugs to patients with life-threatening diseases."

This statement seems to demonstrate the FDA awareness that approving drugs based Phase II single-arm trial data could deliver progress to patients quickly – the central mission of the accelerated approval concept. However, the next comment went in a different direction:

**Slide 3**

"An alternative trial design uses a randomized trial allowing accelerated approval on the basis of an interim analysis of surrogate endpoints, for example, response rate or time to progression."

Anyone who has been following the FDA's policies for cancer drugs knows that this was not an idle comment. It was the first in a new set of policies, in effect a new rule, that would be broadly enforced by FDA oncology reviewers.

**Slide 4**

Next Dr. Pazdur stated that:

"Randomized trials also may optimize the evaluation of novel cytostatic agents by allowing an assessment of slowing or retarding or preventing tumor progression. This may simply not be possible with single arm trials."

We now know this meant that the prospects for approval of new cancer drugs based on single-arm trials were not good.

**Slide 5**

Moving further into the new rule book, Dr. Pazdur said:

"Obviously randomized trials are more expensive than single arm trials and take more time. "

Demonstrating that FDA was aware the new rules would slow translation and increase the costs of that translation for new safe and effective cancer drugs.

**Slide 6**

Moving on he stated:

"Survival analysis can be complicated and confounded by cross over and subsequent therapy."

And sponsors soon found they had little choice but to design and conduct increasingly unethical randomized, double-blind, placebo-controlled clinical trials in refractory patient populations to stay within the "unmet need" requirement for accelerated approval.

**Slide 7**

Dr. Pazdur then made it clear how this was going to work in the context of Phase IV trials:

"The mandatory confirmatory trials to demonstrate clinical benefits are equally important as the initial trials demonstrating an effect on a surrogate endpoint leading to that drugs approval."

FDA was making it clear that the post-approval trials Congress said "may" be required by FDA, will in fact be required every single time. FDA was also making it clear that conduct and completion of those trials will be mandatory every single time, and that failure to comply could result in withdrawal of the drug, notwithstanding an inability to enroll the trial because it was unethical, obsolete or simply impracticable.

**Slide 8**

Then we heard how Decelerated Approval would fit in to FDA's new policy paradigm:

"Hence confirmatory trials must be an inherent and integral part of a comprehensive drug development plan and drug development strategy. "

It meant – do you want your drug approved or not? If you do, then follow the rules.

Although not obvious at the time, it also meant that that FDA would start delaying accelerated approvals until unethical, unnecessary double-blind, randomized, placebo-controlled, and in some cases no cross over Phase III clinical trials could be started, enrolled, and run to an interim analysis point.

**Slide 9**

In fact, the decelerated approval initiative effectively eliminated the accelerated approval pathway as a reasonable option for sponsors to pursue, moving the clinical trial requirements so close to those needed for regular approval that its intent – acceleration – was neutralized.

**Punitive Drug Development and Approval**

**Slide 10**

So what did we get from all of this?

A punitive enforcement program for Phase IV clinical trials and the potential for withdrawal of safe and effective cancer drugs based on any failure to complete the Phase IV trials, or to unequivocally achieve regular approval endpoints.

**Slide 11**

Accelerated Approval would be available only for sponsors whose development program had already achieved substantial compliance with endpoints intended for regular (full) approval.

**Slide 12**

Accelerated Approvals would be denied or delayed to ensure a large, desperate pool of patients facing death from their disease to coerce patients under duress to enroll in marginally and even clearly unethical Phase III clinical trials, thus resolving the Phase IV trial enrollment issues.

**Slide 13**

The Decelerated Approval initiative is in direct conflict with the intent of Congress – the idea to speed up delivery of medical progress to patients who need it to live.

The initiative was conceived and implemented unilaterally by FDA staff over the protests of some stakeholders including the Abigail Alliance.

The policy shifts happened in plain view of agency leadership who cannot legitimately claim they did not understand the implications, because we told them - repeatedly.

And most tragically – many thousands of patients died prematurely, waiting for drugs and medical progress that should have been instead quickly delivered to the clinics.

**Slide 14**

A compelling example of the effect the Decelerated Approval Initiative has had on medical progress and patients is what happened with Bayer's Bay 43-9006, now known as Sorafenib.

Coming out of Phase II in 2003, Sorafenib certainly appeared to be the kind of drug that Congress intended would be eligible for Accelerated Approval – but no Accelerated Approval application was submitted.

Of course we can only speculate why, but I think we can speculate accurately that Bayer received the message that Accelerated Approval was off the table without a randomized trial.

We do know that Bayer negotiated a Special Protocol Assessment with FDA for a Phase III clinical trial. Perhaps finding themselves unable to predict what FDA was up to, they thought that course the only way to exert some control over the future handling of their drug by FDA.

**Slide 15**

The SPA negotiations produced an astoundingly unethical randomized, double-blind, placebo-only controlled, no cross over trial. The result of course, was patients on placebos dying prematurely inside the trial, and patients dying prematurely outside the trial because they couldn't get the drug by any means.

Earlier this year, after an interim review showed that Sorafenib was far better than a placebo, a result that should have been confidently expected by all concerned, Bayer came under intense pressure to allow cross over for the placebo patients who were still alive. A few months later Bayer started an expanded access program, but the delay of nearly two years in making the drug available denied thousands of renal cell cancer patients access to the Sorafenib, and many of them died, waiting.

While this is an especially egregious example, it is far from isolated.

Sorafenib remains unapproved.

**Slide 16**

Fast Forward to the ODAC meeting for Revlimid held on September 14, 2005. More than two and half years after the rollout, the devastating effects of the Decelerated Approval Initiative are on full display.

Revlimid is before the committee with compelling data from two Phase II single-arm trials. Celgene is asking for regular approval in the treatment of a targeted patient population with myelodysplastic syndrome, or MDS.

**Slide 17**

Dr. Richard Pazdur explains FDA's advice to Celgene for before they started the single-arm trial:

"On several occasions, as will be mentioned by the FDA reviewer, we have recommended to the sponsor before they began the study, that we look at randomized studies of this drug in MDS to have a better understanding of the disease in relationship either to other therapies or the natural history of the disease."

Despite the fact that the data is extremely compelling, FDA appears disappointed that a randomized trial was not conducted.

**Slide 18**

Fortunately Celgene kept its own counsel and proceeded with a single-arm, highly ethical trial in a targeted population based on earlier Phase II data. The Phase II trial proved undeniable efficacy in that targeted population.

**Slide 19**

ODAC agreed with Celgene that the drug should receive regular approval and that the proposed risk management plan for the drug is adequate.

**Slide 20**

But FDA seems unsatisfied with the Phase II trials and Dr. Pazdur reminds the ODAC that:

"I want to bring people back to the kind of regulations, and there is a mantra, adequate and well-controlled trials, adequate and well-controlled trials, adequate and well-controlled trials. I am mentioning that three times, because I think that is at the heart of the question here."

Just whose mantra is this and why does it have to be repeated three times? It seems the FDA is saying that safe and effective drugs should not be approved because the conditions of the mantra have not been met? There has been no randomized trial.

**Slide 21**

And then comes a revealing and we think critical exchange between a member of ODAC and a physician presenting for Celgene. Dr. Hussain of ODAC referring to the randomized trial requested by FDA asked:

"And why you chose not to do a Phase III trial when you were asked to do that?"

**Slide 22**

Celgene replied:

"We are going to go to Phase III. We are going to be doing a placebo-controlled trial. I have to say that in discussing that trial with the investigators, there is actually reluctance to put patients on placebo for very long based on the benefit that has been seen here."

**Slide 23**

"The patients who receive placebo, receive that for 4 months. If they are not responding, and we think that essentially, none of them are likely to respond from what we know, then, they will have the opportunity to go on to lenalidomide and continue on that as long as that seems to be benefiting them."

**Slide 24**

On October 3, 2005 only a few days before the FDA's deadline for a decision on Revlimid, FDA decided to extend its review time for a decision on Revlimid, citing new information submitted for the risk management plan – the same risk management plan that was provided to ODAC and judged to be adequate.

**Slide 25**

This exchange turned the relationship and missions of the FDA and the sponsors up side down. The sponsor was looking out for patients and the FDA was attempting to force conduct of an unethical, placebo-controlled trial for a drug that had already clearly shown compelling efficacy in a refractory, terminal patient population.

Just who is protecting who? Isn't it the FDA's job to protect the public from unethical and unnecessary human clinical testing?

**Slide 26**

We have a problem. The Decelerated Approval Initiative has been a misguided, devastating and extreme case of form over substance. In this case the substance shoved into the background was life itself for far too many patients, and stalled progress against cancer in a time when we should have been speeding up and learning new ways to accomplish translation more effectively.

**Slide 27**

We need to deactivate Decelerated Approval, banish inflexible mantras from the FDA's lexicon and get on with ways of improving and speeding up our translation of medical progress to patients.

Doing this will require change, and it also may require overcoming resistance to that change, which is why we have advisory committees, why FDA has an appointed commissioner, and why Congress has oversight authority. We call upon this advisory committee today, and on Acting Commissioner Von Eschenbach and Congress, to act on an expedited basis to make sure Accelerated Approval is reinstated, reactivated and improved. Right now, today, is the time for ODAC to get back to its original purpose. You are not here to support FDA's whims and wanderings – you are here to serve the best interests of patients – and if you don't believe that, you shouldn't be here at all.